UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,322	02/14/2002	David T. Curiel	D6392	8688

7590 10/26/2005

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,322	CURIEL ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/05 has been entered.

Claims 1, 4-7 and 10-12 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C., first paragraph, is withdrawn in light of Applicant's amendment.

Claim Objections

Claim 7 is objected to because of the missing of an article "an" in front of the term "adenoviral vector" on line 13 of the claim. Appropriate correction is required.

Unfortunately, upon further review of the application following are new grounds of rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

In claim 1 and its dependent claims, the term "said vector" on line 5 in step (i) and on line 11 in step (ii) renders the claims indefinite. This is because which vector? The transductionally and transcriptionally modified adenoviral vector or the adenoviral vector without the modifications. The examiner suggests the replacement of the term "said vector" with - - the modified adenoviral vector - -.

Similarly, the term "The adenoviral vector" renders the claims 4-6 indefinite because it is not clear which adenoviral vector that Applicants refer to. The examiner suggests the replacement of the term "The adenoviral vector" with - - The modified adenoviral vector - - to overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a). ***This is a reinstated and modified rejection with a new ground of rejection.***

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. (WO 98/40508; Cited previously) in view of Muzykantov et al. (Am. J. Physiol. 270: L704-L713, 1996; IDS).

Sosnowski et al. disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al further teach that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and

smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Sosnowski et al. do not teach specifically the utilization of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system.

However, at the effective filing date of the present application Muzykantov et al. already disclose that the Mab 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration, and that Mab 9B9 is internalized by endothelial cells both *in vitro* and *in vivo* without significant intracellular degradation (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the retargeted, tropism-modified adenoviral vector system of Sosnowski et al. by utilizing a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, and more specifically the bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody to target the modified adenoviral vector containing a transgene specifically to pulmonary vascular endothelium after a systemic delivery in light of the teachings of Muzykantov.

An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a **safe, specific** and **useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration** and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that **any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob**. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Sosnowski et al. and Muzykantov et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 5/24/04 (pages 10-13) have been fully considered, but they are not found persuasive.

1. Applicants note that Sosnowski et al teach that FGF-2 mediated enhancement in gene expression was due to infection of greater percentage of target cells, but in fact Sosnowski et al teaches that FGF-2 adenoviral vector induced 12 to 20-fold less transgene expression in the liver than non-retargeted adenoviral vector, while Muzykantov et al contemplate the use of Mab 9B9 for selective intracellular delivery of drugs to the pulmonary vascular endothelium after systemic administration. Applicants argue that neither of the two cited references have contemplated or expressed the need to combine the two different techniques. In fact, based on the teachings and the successes of Sosnowki et al. and Muzynkantov et al., a person having ordinary skill in

the art would simply not motivated to replace or combined the two techniques taught by two references.

Firstly, please note that FGF2-Ad induced 12-20-fold less transgene expression in the liver than non-retargeted Ad (page 163, lines 8-10) **is precisely the desired and expected result** for the re-targeted, tropism-modified FGF2-Ad because liver is the non-targeted tissue. FGF2-Ad abrogates successfully the liver tropism of unmodified adenovirus.

Secondly, it should be noted that this is a 103 rejection, and therefore each cited reference does not have to teach every element of the claims. An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a **safe, specific** and **useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration** and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that **any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob**. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting

enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells.

2. Applicants also argue that all of the elements of the present invention are not taught by combination of the two references, and that it is well known in the art and also discussed in Sosnowski et al (page 28, lines 3-9), any attempt to modify the adenovirus vector should not affect the vector's ability to attach to specific receptors of target cell, get internalized and transfer the gene to the nucleus to be expressed. Hence, combining the teachings of two references does not guarantee success in the use of the vector of the present invention.

Firstly, the examiner does not understand which specific element of the present invention that Applicants alleged that the combined teachings of Sosnowki et al. and Muzykantov et al. Please be specific and please read the above rejection.

Secondly, with respect to Applicant's doubt on the expected success of the combined teachings of Sosnowki et al. and Muzykantov et al., please refer to the successes already demonstrated by Sosnowski et al. (WO 98/40508). It is further noted that the results of Sosnowski et al. (WO 98/40508) are the same results present in U.S. Patent 6,613,563 that has claims drawn to a tropism-modified adenoviral vector system that specifically targets cells expressing a preselected receptor, wherein the adenoviral vector contains a tissue-specific promoter operatively linked to a nucleic acid molecule that encodes a gene product, and wherein the gene product enhances cellular proliferation or cellular differentiation (see claims 1-7 of the issued U.S. Patent). Muzykantov et al. also demonstrated clearly that the Mab 9B9 to angiotensin converting

enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration.

Accordingly, claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. (Mol. Ther. 2: 562-578, 2000) in view of Sosnowski et al. (WO 98/40508; Cited previously). ***This is a new ground of rejection.***

Reynolds et al disclose a targetable, injectable adenoviral vector for selective gene delivery to pulmonary endothelium *in vivo*, said vector comprises a bispecific antibody (Mab 9B9 conjugated to 1D6.14 anti-knob Fab antibody) that target Ad infection specifically to angiotensin-converting enzyme, which is preferentially expressed on pulmonary capillary endothelium (see abstract and the Methods section). Reynolds et al further teach that administration of retargeted vector complex via tail vein injection into rats resulted in at least a 20-fold increase in both Ad DNA localization and luciferase transgene expression in the lungs, compared to the untargeted vector. Additionally, targeting led to reduced transgene expression in nontarget organs, especially the liver, where the reduction was over 80%. Reynolds et al. also state that "However, further refinements to avoid nonspecific uptake of vector by the reticuloendothelial system may be required for optimal efficacy" (page 577, col. 1, bottom of second paragraph).

Reynolds et al do not specifically teach the use of any tissue specific promoter, including the vascular endothelial growth factor type I receptor promoter, in the disclosed adenoviral vector for expressing a transgene.

However, at the effective filing date of the present application Sosnowski et al. already disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al teach specifically that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues to line 19 of page 76).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the targetable, injectable adenoviral vector system of Reynolds et al. by also incorporating the use of an endothelial cell specific promoter such as VEGF-receptor promoter in light of the teachings of Sosnowski et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Sosnowski et al already teach **the use of an endothelial cell specific promoter provides an extra margin of specificity** (page 75, lines 3-5), and that this would be a refinement that avoids the nonspecific uptake and non-specific expression of a transgene in non-targeted cells *in vivo*.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Reynolds et al. and Sosnowski et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

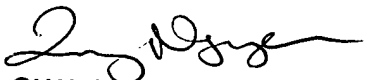
If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Quang Nguyen, Ph.D.



QUANG NGUYEN, PH.D
PATENT EXAMINER